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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,757	02/08/2001	Yechezkel Barenholz	BARENHOLZ=1	6619

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Browdy and Neimark
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EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 08/14/2002

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/780,757

Applicant(s)

BARENHOLZ ET AL.

Examiner

Jeffrey Fredman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 July 2002.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19-36 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 19-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zuidam et al (Biochim. Biophys. Acta (1998) 1368:115-128) in view of Gee et al (U.S. Patent 5,830,912).

Zuidam teaches a method for determining binding of a nucleic acid biomolecular species at a lipid surface having a local environment at a given pH or surface potential wherein the binding is effective to alter said pH or potential (abstract) comprising the steps:

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(a) incorporating at said surface a probe, here 4-heptadecyl-7-hydroxycoumarin, which comprises a potential and pH sensitive fluorophore attached to a lipid (page 117, subheading "liposome preparation"),

(b) observing a change in a fluorescent property of said fluorophore upon binding of said nucleic acid species to said lipid bilayer with cationic head groups (see page 117, figure 1 for observational data and page 117, column 1 for cationic nature of liposomes)

Zuidam further teaches a biomolecule with groups which are charged at pH between 4.5 and 7.5 and a surface which is also charged in this pH range (see page 117, column 1, with Hepes at pH 7.4).

The hydroxycoumarin label of Zuidam will be necessarily buried within the lipid bilayer due to the presence of the alkyl chain.

Zuidam does not teach the probe having two alkyl chains of 14 carbons in length, nor does Zuidam teach that the lipid is a phospholipid.

Gee teaches a composition which is a fluorescent probe, comprising a coumarin fluorophore linked to a phospholipid with two alkyl chains of greater than 14 carbons in length (see column 11, compound 68) and suggests the use of this compound in interactions with lipoproteins (column 23, lines 23-28). Guo teaches the use of DNA, proteins, hormones and steroids as conjugates (see column 14, lines 58-67, column 24, table 4).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the probe of Gee in the method of Zuidam since

Gee states "Dye compounds that possess a lipophilic substituent at R3 or R4 or that are conjugated to lipophilic molecules such as phospholipids will noncovalently incorporate into lipid assemblies, e.g. for use as probes for membrane structure or for incorporation in liposomes, lipoproteins, films plastics, lipophilic microspheres or similar materials (column 23, lines 23-28)." Thus, an ordinary practitioner would have been motivated to use compound 68, with it's lipophilic substituents, in the method of Zuidam in the place of 4-heptadecyl-7-hydroxycoumarin as a probe for membrane structure and incorporation into liposomes since Gee teaches that these are useful in those methods.

Response to Arguments

4. Applicant's arguments filed July 18, 2002 have been fully considered but they are not persuasive.

Applicant argues that the Zuidam reference cannot render the claim obvious because the label incorporated by Zuidam is unstable, while the claim requires "stable incorporation" which is defined on page 6 of the specification as "low desorption rate from the bilayer". This argument is not persuasive for several reasons.

First, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, since the probe of Gee would meet the stable incorporation limitations, the argument that Zuidam lacks this teaching fails to properly combine the references.

Second, the claim limitations, whether based upon the phrase "stably incorporated" or its definition in the specification "low desorption" are relative terms. The specification does not provide a standard for ascertaining the requisite degree of "stability" or "desorption" required to meet the claim because no specific levels are identified in the specification. Thus, when the claim is read broadly, any period of time in which the label is incorporated constitutes a stable incorporation and any desorption rate constitutes a low desorption rate, when there is no absolute value provided to define the scope and meaning of these terms. Therefore, when the limitation of "stably incorporated" is read broadly, Zuidam would meet this limitation.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation to combine is cited in the rejection. Specifically, it is noted that Gee expressly suggests that his compounds can be used as membrane probes in methods such as Zuidam. As Gee is quoted above noting that his compounds are "for use as probes for membrane structure (column 23, lines 23-28). Since the entire goal of Zuidam is probing membrane structure, Gee expressly motivates the use of his compound in the preferred embodiment of Zuidam.

Applicant then argues this is an "obvious to try" situation. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e. , a reasonable expectation of obtaining similar properties. See , e.g. , *In re O'Farrell* , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art that the probes of Gee be used as membrane probes (see column 23). There is further evidence as shown by Gee in 48 different examples where a series of different analogs are made and each is shown to function (see columns 25-41). Further, Zuidam shows labels functioning in the analytical method (see page 119, figure 3). This sufficient for a reasonable expectation of success. The MPEP cites *In re O'Farrell*, which notes regarding "obvious to try" at page 1682, that,

"In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g. , *In re Geiger* , 815 F.2d at 688, 2 USPQ2d at 1278; *Novo Industri A/S v. Travenol Laboratories, Inc.* , 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); *In re Yates* , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); *In re Antonie* , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *In re Dow Chemical Co.* , 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); *Hybritech, Inc. v.*

Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1986), cert. denied, 107 S.Ct. 1606 (1987); In re Tomlinson; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters or only general guidance is given, since the prior art of Guo directly points to the use of compound 68 in studies on membranes

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.


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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Jeffrey Fredman
Primary Examiner
Art Unit 1637

August 12, 2002